REMARKS

Claims 1-13 have been cancelled. Claims 13-38 have been added to merely clarify the present invention. All of the newly added claims are fully supported by the disclosure in claims as originally filed. In particular, attention is directed to pages 5, 7, 8, 13 and 17-19 of the present specification.

Request for Reconsideration

The administration of active pharmaceutical ingredients by inhalation has been used and recognized as a valuable mode of delivery for many years. With such a mode of delivery, smaller quantities of active ingredient may be used since drug action occurs directly on the target organ as compared to when oral delivery is used. Three delivery systems have been used for pulmonary administration, although each has significant drawbacks.

First, nebulizers have been used in pulmonary administration of active pharmaceutical ingredients, but tend to be expensive, bulky and require long periods of administration. Consequently, nebulizers are primarily used in hospitals.

Second, pressurized metered dose inhalers (PMDIs), although popular for the last two decades, require a difficult coordination between actuation and inhalation. Presently, such devices are not viewed favorably as they have used chloroflurocarbons (CFCs) as propellant gases.

Third, dry powder inhalers (DPIs) provide a fine cloud of drug particles to the patient and the quantity of drugs provided to the lungs depends on the air flow of the patient. Generally, it is considered that in order to reach the lungs, a particle size of less than 6 μm must be used; while a particle size of less than 2 μm is required in order to reach the deep regions of the lungs, i.e. bronchioles and alveoles.

In fact, lung deposition of the drug administered with a DPI is influenced by three parameters, which are (a) the patient, (b) the device, and (c) the formulation. As for the patient, the formulator must guarantee that the category of patients targeted will have a sufficient respiratory

capacity to allow the desired amount of drug to reach the lung. Of course, the inhalation system must be simple for the patient to use.

The ideal inhalation device is simple to use, portable, inexpensive, and able to provide multi-doses in a reproducible way. Further, the ideal inhalation device must protect against possible overdosage.

The formulation must contain a powder with a high percentage of respirable particles. The parameters influencing in lung deposition are the nature, size, shape and surface properties of the carrier particles as well as the ratio between the active ingredient and the carrier as well as the total amount in the capsule or in the dosing chamber. Humidity and electro-static forces are also important factors. Further, an inert water-soluble, free-flowing course excipient has been used, and most often α-lactose or another mono- or dissaccharide has been used.

Unfortunately, the individual particles of excipient are modified in conventional techniques such as crystallization, spray drying and precipitation, and crystalline excipients prepared in these manners do not bind the active ingredient sufficiently strongly and, accordingly, generally provide a mixture which is unstable and which segregates during handling and filling. At the same time, excipients having a rugosity of greater than 2.0, provoke a partially irreversible bond with the pharmaceutically active material with which it is formulated leading to inaccurate dosages upon administration.

Advantageously, the present invention provide a form of particulate pharmaceutically excipient for use in a dry powder inhaler composition. The excipient not only allows a high dose of active ingredient to be delivered to the lungs, but also provides low variation of delivery.

In particular, the present invention provides in part, dry powder inhaler pharmaceutical composition containing a mixture of a particulate pharmaceutical active ingredient in a particulate roller-dried and β-lactose excipient.

The present invention also provide, in part, a process for the preparation of a dried powder

inhaler of pharmaceutical composition containing a mixture of a particulate pharmaceutically-active ingredient in a particulate roller-dried and hydros β-lactose excipient, in which a dry particulate pharmaceutical active ingredient is mixed with a particulate roller-dried and hydros β-lactose excipient.

Claims 1-3 stand rejected under 35 U.S.C. 102(b) as anticipated by Stevenson (U.S. 4,199,578). However, it is clear that this reference fails to either disclose or suggest the present invention.

Notably, Stevenson discloses a pharmaceutical composition containing a mixture of particles of bethamethasone dipropionate and a powder carrier, the composition being, for example, dispersed by means of an inhalation device into the inhaled air stream. Stevenson describes that the carrier has a particle size below 400 μm and may be any non-toxic material which is chemical inert to bethamethasone dipropionate. Possible carriers exemplified are calcium carbonate, calcium lactate, maltose, sucrose, polysaccharides, starches and dextrins. A preferred carrier is lactose, e.g. crystalline lactose.

Importantly, this reference fails to disclose or suggest the use of roller-dried anhydrous β-lactose excipient nor does it describe or suggest the advantage of using such an excipient in a dry powder inhaler pharmaceutical composition. Thus, one skilled in the art would not be put in possession of the present invention by this reference.

Hence, this ground of rejection is believed to be unsustainable and should be withdrawn.

Claims 1-3 stand rejected under 35 U.S.C. 102(a) as anticipated by Baichwal et al. (U.S. 5,612,053). However, this reference also fails to either disclose or suggest the present invention.

In particular, Baichwal et al. describe a controlled release powder insufflation formulation containing a medicament and a controlled release carrier which preferably includes one or more polysaccharide gums of natural origin. The medicament is granulated with the polysaccharide and, optionally, a polysaccharide filler, such as lactose, may be added.

However, it is clear that this reference fails to disclose or suggest the inclusion of a particulate roller-dried anhydrous β-lactose excipient. Neither does the reference disclose or suggest the advantages of using such an excipient in a dry powder inhaler pharmaceutical composition. Hence, one skilled in the art would not be put in possession of the present invention by this reference.

Hence, this ground of rejection is believed to be unsustainable and should be withdrawn.

Claim 4 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Ganderton et al. (U.S. 5,254,330) in view of Ganderton et al. (U.S. 5,376,386). However, it is clear that neither reference, either alone or in combination with the other, discloses or suggests the present invention.

At the outset, it is noted that Ganderton et al. (both '330 and '386) correspond to WO 91/11179 cited in the corresponding European application and to CA 2,049,302, cited in the corresponding Canadian application.

In particular, both Ganderton et al. references describe the use of particulate crystalline sugars such as lactose monohydrate having a rugosity of less than 1.75. Moreover, the crystalline lactose monohydrate used in both Ganderton et al. references, is not roller-dried.

In fact, roller-dried anhydrous β-lactose used in the present invention has a high rugosity between about 1.9 and 2.4 due to the rolled-drying process.

Both the Ganderton et al. references teach the importance of using a carrier having a low rugosity, i.e. a rugosity of less than 1.75, in order to have improved redispersion of drug particles. Both Ganderton et al. references show that when using regular lactose (i.e. a lactose having a rugosity of more than two), the amount of drug particles deposited at stages 3-7 (particles with the size of less than 5.5 micrometers) i.e. fraction contained in particles suitable for a long deposition, is at least two times lower than the amount of drug particles deposited in stages 3-7 when using crystallized lactose having a rugosity of 1.16.

Thus, both Ganderton et al. references will be understood by one skilled in the art to teach a lactose having a low rugosity (see column 2, lines 23-36), however, when using the lactose with a high rugosity, a very low long deposition is achieved.

Thus, both the Ganderton et al. references would clearly teach away from the present invention as they would strongly discourage one skilled in the art to use a lactose carrier having a rugosity of more than 2. One skilled in the art would understand that if a lactose carrier had a rugosity of more than 2 were used, only a low deposition would be achieved in stages 3-7, i.e. in the lung. This would be considered undesirable.

Furthermore, one skilled in the art would be unable to predict – and would not expect – that by using a specific excipient having a rugosity not suitable according to the Ganderton et al. references, that it would be possible to achieve a higher deposition of the drug in the lung. The mere fact that the present invention makes such results possible is on its face, i.e. prima facie, surprising.

The present specification shows that by using rolled-dried anhydrous β-lactose, it is possible to achieve a higher pulmonary fraction than when using crystalline α-lactose or spray-dried lactose monohydrate. Clearly, one skilled in the art would have no reason to expect or to predict that it would be possible to increase the pulmonary fraction by using only one specific excipient. For example, in accordance with the present invention, when using rolled-dried anhydrous β-lactose with a particle size of between 100 and 160 μm, it is possible to increase the pulmonary fraction of about 50% with respect to the pulmonary fraction achieved when using spray-dried lactose as excipient. (See Table 2)

Additionally, Example 1 and Table 1 of pages 9 and 10 of the present specification demonstrate that the roller-dried anhydrous β-lactose of the present invention affords a superior deposition of active ingredient as compared to crystalline α-lactose.

Example 2 and Table 2 at pages 11 and 12 of the present specification evidence the

surprisingly superior deposition of active ingredient afforded by roller-dried anhydrous β-lactose particles having a particle size of from 100-160 μm.

Table 3 at page 13 of the present specification evidences that the roller-dried anhydrous β-lactose particles of the present invention allow almost no lactose to be deposited in the lungs. Lung deposition of lactose occurring with conventional formulations is considered to be responsible for the irritant effects of conventional DPI formulations.

Thus, the present dry powder formulation enables a good lung deposition (>30%), with good lung penetration of the active ingredient. However, there is practically no deposition of excipient.

Thus, on the basis of evidence in the present specification and the teachings of both Ganderton et al. references to the contrary, it is clear that the present invention would not have been obvious to one skilled in the art at the time the present invention was made.

Hence, this ground of rejection is believed to be unsustainable and should be withdrawn.

Claims 2, 4, 10, 11 and 13 stand objected to for the two reasons noted at page 2 of the Official Action.

However, in view of the above amendments, these objections are deemed moot.

Accordingly, in view of all of the above, it is believed that the present application now stands in condition for allowance. Early notice to this effect is earnestly solicited.

An Information Disclosure Statement will be filed separately.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 07-1337 and please credit any excess fees to such deposit account.

Respectfully submitted,

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